REMARKS

Claims 1-9 and 32-49 remain pending. Claims 50 and 51 have been added, depending from claim 49, with each of claims 50 and 51 having all the limitations of claim 49 but only one of the alternative libraries of claim 49.

REJECTION OF CLAIMS UNDER 35 U.S.C. §103(a)

RECONSIDERATION IS REQUESTED OF THE REJECTION OF CLAIMS 1-4, 6-9, 32-34, 37-43, 45-47, AND 49 UNDER 35 U.S.C. § 103(A) OVER GOUGH ET AL. IN VIEW OF KODACEK ET AL. AND PETRENKO ET AL.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.[1]

Gough et al.

Gough et al. describe identification of antibodies specific for surface-exposed epitopes on germlings of certain species of *Phytophthora* to be used for production of immunological probes and scFV antibodies which interfere with the infection process.[2] Gough et al. does not disclose phage display of a random peptide library or the selection of non-immunoglobulin peptides that bind epitopes on the surface of fungus, as required by the presently claimed subject matter.

Gough et al. use only scFV antibody fragments in their disclosed phage display methods. Gough et al. report no problems associated with using antibody fragments in the disclosed phage display methodology for the purposes they pursued. Gough et al. do not suggest using peptides rather than antibody fragments in the disclosed methods. In fact, substituting peptides for antibody fragments in the method of Gough et al. would be unproductive in that Gough et al. seek to identify antibodies and not mere peptides.

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[1] MPEP § 2143.01.

As illustration, Gough et al. states that "it remains an important goal to develop non-macromolecular species **that retain the favorable molecular recognition characteristics of antibodies**, but can be identified quickly and easily and synthesized in large amounts." Similarly, Gough et al. state that "the isolation of other **scFVs** [antibody fragments] specifically directed against the native conformation of surface-accessible **antigens** may well provide new tools to probe and manipulate pathogenicity."

To accomplish the objectives of Gough et al. (*i.e.*, to isolate antibodies to surface antigens for use as immunological probes), one skilled in the art **could not modify** the disclosed methods so as to substitute random peptides (*i.e.*, non-immunological) for scFVs.

Kodacek et al.

Kodacek et al. describe an assay to identify phage displayed specialized "pincer" peptides with high binding affinity for a single target peptide. Kodacek et al.'s "pincer concept" method involves (i) construction of a phage display library where the displayed peptides have a protease site near the N-terminus; (ii) cleavage of the displayed peptide to expose the N-terminal serine, (iii) oxidization of the exposed N-terminal serine to an aldehyde after cleavage; (iv) formation of a heterodimeric binding molecule (*i.e.*, a "pincer") by attachment of an O-amino derivative of the genetically selected lead peptide to the aldehyde via oxime formation; and (v) panning the so-formed phage displaying the "pincer peptide" against a specific individual target peptide.[3] This specialized approach facilitated identification of peptide-peptide interactions that were too unstable when either antibodies or simple peptides were displayed on the phage.

Put simply, Kodacek and Gough et al. cannot be combined without violating the objective of either reference. Kodacek et al. suggest the superiority of their specialized pincer peptides. Further, simple peptides and antibodies are both inadequate for Kodacek et al.'s purpose. In contrast, Gough et al. seek antibodies. Kodacek et al. and

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[2] Gough et al., at 98.
[3] Kodacek et al., U.S. Ser. No. 20010029024, at ¶ 132; *see id.* at ¶ 25.

Gough et al. represent mutually exclusive domains and any suggestion of substitution of the specialized peptides of Kodacek et al. into the methods of Gough et al. would not work. Thus, one skilled in the art could not substitute the highly specialized O-amino derivative displayed peptides or the single target peptide into the methods of Gough et al. without violating the objective of the base reference of Gough et al.

The Office asserts that Kodacek et al., by describing the disadvantages in the use of antibodies in binding studies, provided the motivation to one skilled in the art to substitute simple peptides into the methods of Gough et al. But the prior art must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claims.[4] The Office fails to point out that Kodacek et al. also disclose similar disadvantages of peptides: "Unfortunately, peptides, or peptide epitopes in proteins, are difficult targets for molecular recognition studies in aqueous solution."[5] While Kodacek et al. disclose some drawbacks to the use of antibodies in binding studies, Kodacek et al. also say that "**advances in single chain antibody libraries [scFVs] on phage** (Griffiths and Duncan, 1998; Rader and Barbas, 1997) **promise to speed up this process.**"[6] Thus, disadvantages of antibody usage are suggested to be minimized by the phage display methodology. No such claim was made for peptides. Rather, Kodacek et al. disclose that previous efforts of the inventors to identify small molecular weight peptides that bound to surface epitopes by employing well-established methods of phage display "**failed completely.**"[7] To overcome the limitations and prior failures, Kodacek et al. resorted to the specialized "pincer" peptides on phage to pan against a single target peptide (as described above) rather than panning simple peptides against a multitude of surface exposed epitopes.[8] Thus, Kodacek et al. leads away[9] from the

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[4] MPEP § 2141.02.
[5] Kodacek et al., at ¶ 6.
[6] *Id.* at ¶ 9.
[7] *Id.* at ¶ 38.
[8] *Id.* at ¶ 39.
[9] A reference teaches away when it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. *See U.S. v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990).

substitution of small molecular weight peptides for antibody fragments in the phage display methods of Gough et al. given Kodacek et al.'s failure with this type of approach.

Petrenko et al.

Petrenko et al. disclose the selection of phage with complex surface functions that would be useful in nanotechnology applications. According to Petrenko et al., these complex surface functions of phage clones depend on interactions between neighboring groups of display peptides and wild type peptides. These emergent properties of the phage surface inhere to the entire surface of the phage, rather than in the peptides of the library themselves. As an example, Petrenko et al. suggest as desirable a phage with a high affinity for a metal ion that displays metal complexed on the surface in a specific repeating geometry. Petrenko et al. specifically disclose experiments where phage clones were selected for the global property of chloroform resistance. Petrenko et al. also disclose panning phage displayed peptides against a single target molecule. Such single targets included dioxin in one experiment and the lectin Concanavalin A in another experiment. In both cases, the phage displayed library of peptides was panned against a single known target, not a surface composed of a multitude of targets.

Modifying the methods of Gough et al. according to that disclosed in Petrenko et al. would fail to achieve the objectives of either reference. Gough et al. sought to identify specific antibodies that bind any one of a multitude of epitopes on the surface of *Phytopthora*. Petrenko et al. sought to identify phage clones that exhibited global properties such as chloroform resistance without regard to particular peptides of the library. Even where Petrenko et al. identified peptides that bound to a target, the target was a single well characterized molecule. In contrast, the target of Gough et al. was a multitude of unknown epitopes present on the surface of a *Phytophthora*. Nowhere in Petrenko et al. is there any indication of how the local properties of phage-peptide would provide advantage over the local properties of phage-antibody fragments; it is not enough that peptide libraries, or specifically the f8-1 peptide library, *could be*

theoretically substituted into the methods of Gough et al.[10] Thus, one skilled in the art would not be motivated to modify the methods of Gough et al. according to Petrenko et al. because of incompatible objectives and a lack of any suggestion of advantage or desirability to do so.

The Office points to Petrenko et al.'s extolling of the "global functions" that inhere in the entire surface landscape of phage-peptide as motivation to substitute peptides for antibody fragments in the method of Gough et al. But as stated above, the objectives of Petrenko et al. and Gough et al. are too disparate for one skilled in the art to make such a substitution for it would fail to accomplish the goals of either reference. The global functions described in Petrenko et al. were a means to select phage clones that were sensitive to chloroform and to demonstrate that chloroform resistance of the phage depended upon the global surface properties of the phage. For example, in Petrenko et al., the mosaic phage was up to 10,000 times more sensitive to chloroform than the corresponding non-mosaic phage. In contrast, the present application is directed to identification of particular peptides (displayed on the phage surface) that have a binding affinity for epitopes displayed on the surface of a *Phytophthora* fungi—This goal does not implicate "global functions" that inhere in the entire surface landscape of phage-peptide. Contrary to the Office's assertion otherwise, the mosaic nature of phage-peptide displayed libraries in Petrenko et al. provides neither suggestion nor motivation to substitute peptides for antibody fragments in the method of Gough et al. in order to identify specific peptides with affinity for surface epitopes of *Phytophthora*.

Summary

In summary, the objectives of Gough et al., Kodacek et al., and Petrenko et al., cannot be reconciled with one another. Gough et al.'s objective is to identify antibodies that bind to a large number of unknown epitopes on the surface of *Phytopthora*. The objective of Kodacek et al. is to identify specialized pincer peptides that bind a single known target peptide. And Petrenko et al.'s objective is to identify phage clones that exhibit surface properties useful to nanotechnology applications and to identify peptides

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[10] *See* MPEP § 2143.01 (The mere fact that references can be combined or modified does not

that bind to a single known non-peptide target molecule. Furthermore, these references, either individually or in combination, do not lead to phage displayed random peptide panning against multiple unknown surface epitopes of fungus to select non-immunoglobulin peptides that bind to said epitopes, as required by the claimed subject matter. Thus, there exists no motive or suggestion to combine these references. In the absence of such motivation or suggestion, the Office is prohibited from using the claimed invention as template to piece together the teachings of the prior art, and as such, claims 1-4, 6-9, 32-34, 37-43, 45-47, and 49 are nonobvious.

RECONSIDERATION IS REQUESTED OF THE REJECTION OF CLAIMS 44 AND 49 UNDER 35 U.S.C. § 103(A) OVER GOUGH ET AL. IN VIEW OF KODACEK ET AL., PETRENKO ET AL., AND APPLICANT'S DISCLOSURE OF KNOWN PRIOR ART

The Office asserts that one would be motivated to use "phage f88-4" because of the presence of two genes with a mosaic pattern of wild-type and recombinant pVIII. Claims 44 and 49 contain the feature of an **f88-4 peptide library being expressed on the surface of a vector**. These claims do not require a specific phage as put forth by the Office.

Furthermore, claims 44 and 49 do not rely upon the mosaic pattern of phage coat expression. Emergent properties that inhere in the entire surface architecture may be useful where Petrenko et al. is trying to identify phage clones resistant to chloroform, but it remains unclear how such emergent properties would benefit claims 44 and 49 of the present application. The Office fails to explain how the mosaic pattern, described and used by Petrenko et al., would provide an advantage in the identification of peptides with affinity for surface epitopes of *Phytophthora* fungi. Without such advantage there is no motivation to modify the methods of Gough et al.

The Applicant's disclosure of the known prior art provides no motivation or suggestion to substitute small molecular weight peptides for antibody fragments in the phage display methods of Gough et al. The mere fact that the prior art may be modified does not make the modification obvious unless the prior suggested the desirability of

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render the resultant combination obvious unless the prior art suggests the desirability of the combination).

the modification.[11] While use of the f88-4 peptide library in phage display was known to the art, it was nevertheless nonobvious to use such f88-4 phage-displayed peptide library to pan against surface exposed epitopes on *Phytophthora* species. The number of displayed peptides, the two pVIII genes, and the mosaic pattern of wild-type and recombinant pVIII subunits in an f88-4 phage-displayed peptide library, as disclosed in the specification and quoted by the Office, provides neither suggestion nor motivation that these features would facilitate panning against the exposed surface of *Phytophthora*. Again, without such advantage, there is no motivation to modify the methods of Gough et al.

RECONSIDERATION IS REQUESTED OF THE REJECTION OF CLAIM 5 UNDER 35 U.S.C. § 103(A) OVER GOUGH ET AL. IN VIEW OF KODACEK ET AL., PETRENKO ET AL., AND SMITH.

Because the subject matter of the base claim is nonobvious, the subject matter of dependent claim 5 would thus also be nonobvious. Additionally, claim 5 contains features that are patentably distinct over claims upon which it depends. Claim 5 is as follows:

> The method of any one of claims 1 or 48, wherein the sequence of said random oligonucleotide **is** GCA GNN (NNN)7 or SEQ ID NO: 1.

This claim does not employ open language such as "comprising," instead requiring that the random peptide **is** the disclosed sequence. Petrenko et al. discloses the following nucleotide sequence insert : GCT GCA Gnk (nnk)6 nnG GAT CCC.[12] Based upon this nucleotide sequence, the Petrenko et al. insert contains 11 peptides, with Asp and Pro (*i.e.*, non-random) at the 3' terminus. In contrast, the sequence of claim 5 encodes but 9 peptides with the two 3' terminal peptides being random. The Office asserts that Smith teaches the use of fully degenerate codons (nnn) in the variable region of the oligonucleotides of the library. But Smith never suggests why the sequences of Petrenko et al. should be modified. That is to say, the Office provides no

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[11] *See* MPEP § 2143.01.
[12] Petrenko et al., at Fig.1A.

motivation or suggestion to modify the Petrenko et al. sequence from 11 peptides to 9 peptides or to make the last two 3' terminal peptides random.

RECONSIDERATION IS REQUESTED OF THE REJECTION OF CLAIMS 35, 36, AND 48 UNDER 35 U.S.C. § 103(A) OVER GOUGH ET AL. IN VIEW OF KODACEK ET AL., PETRENKO ET AL., AND QUI ET AL.

Claims 35 and 36 both depend from claims 1 or 49 and are patentable over the prior art as discussed above and additionally contain features that are patentably distinct over the subject matter of claims from which it depends. Furthermore, claim 48 is patentable and nonobvious. The arguments made above with respect to Gough et al., Kodacek et al., and Petrenko et al. apply here as well.

Qui et al. would not motivate one to use the species of *Phytophthora* listed in claims 35, 36, and 48 in the method of Gough et al. The stated objective of Qui et al. is to impart pathogen resistance to plants by applying a hypersensitive response elicitor polypeptide to a plant seed. In the context of Qui, elicitors are polypeptides or proteins able to elicit local necrosis in plant tissue (*i.e.*, hypersensitive response) contacted by the elicitor. The elicitor-receptor-mediated hypersensitive response is a widely distributed pathogen defense mechanism known to occur across a variety of fungal, bacterial, and plant species. Qui et al. state that the elicitor polypeptide can be "derived from **a wide variety of fungal and bacterial pathogens**," a few examples of which include *Erwinia*, *Pseudomonas*, *Xanthamonas*, and *Phytopthora*.[13] Just because a wide variety of fungal and bacterial pathogens can elicit a hypersensitive response in plants would not motivate one skilled in the art to conclude that the same variety of species would behave similarly for other, unrelated traits. The Qui et al. patent does not suggest that any of the numerous species capable of triggering a hypersensitive response in plants would be desirable in the methods of Gough et al. In other words, while Qui et al. provided various species of *Phytophthora* as examples of sources of elicitor polypeptides, this disclosure would not motivate one skilled in the art to substitute various *Phytophthora* species into the methods of Gough et al. just as it

[13] Qui et al., U.S. Patent No. 6,235,974, col. 7, ln. 5-10.

would not motivate one skilled in the art to substitute species of *Erwinia*, *Pseudomonas*, *Xanthamonas*, or any other group of organisms known to elicit a hypersensitive response.

CONCLUSION

Applicants appreciate the Office's thorough consideration of the subject application, as amended. In light of the foregoing, Applicants request an entry of the claim amendments, request a withdrawal of claim rejections, and solicit allowance of the claims. The Office is invited to contact the undersigned attorney should any issue remain unsolved.

The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,

Edward J. Hejlek, Reg. No. 31,525
SENNIGER POWERS
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

DJH/lrw
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